Blood pressure, vessels and drug intervention: "To help or at least to not harm"

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HABILITATIONSSCHRIFT

Blood pressure, vessels and drug intervention: "To help or at least to not harm"

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Vorwort

Die nachfolgend angeführten und beigelegt Originalarbeiten werden als kumulative Habilitationsschrift eingereicht.

1. Sudano I, Virdis A, Taddei S, Spieker L, Corti R, Noll G, Salvetti A, Luscher TF. Chronic Treatment With Long-Acting Nifedipine Reduces Vasoconstriction to Endothelin-1 in Essential Hypertension. Hypertension 2007. 49: 285-290

2. Flammer AJ*, **Sudano I***, Hermann F, Gay S, Forster A, Neidhart M, Künzler P, Enseleit F, Périat D, Hermann M, Nussberger J, Lüscher TF, Corti R, Noll G, Ruschitzka F. Angiotensin converting enzyme Inhibition improves vascular function in rheumatoid arthritis. Circulation 2008. 29; 117(17):2262-2269. * both author contribute equally to this paper.

3. **Sudano I***, Flammer AJ, Periat D, Enseleit F, Hermann M, Wolfrum M, Hirt A, Kaiser P, Hurlimann D, Neidhart M, Gay S, Nussberger J, Mocharla P, Landmesser U, Haile SR, Corti R, Vanhoutte PM, Lüscher TF, Noll G, Ruschitzka F. Acetaminophen increases Blood Pressure in Patients with Coronary Artery Disease. Circulation. 2010 Nov 2;122(18):1789-96

Summary

The pathological elevation of arterial blood pressure is one of the most important cardiovascular risk factors deserving a careful monitoring by patients and medical doctors.

Dysfunctional vessels and blood pressure values are strictly related in a dangerous vicious circle.

When prescribing drugs we should be sure we should keep in mind that beyond their primary effect they could have positive as well negative ancillary effects. Using antihypertensive drugs we should consider not only the blood pressure effect but also check if they modified vascular function; cardiovascular drugs may have beneficial effect in patients with non-cardiovascular disease and last but not least non-cardiovascular drugs may influence the cardiovascular risk profile of our patients.

1. Chronic Treatment With Long-Acting Nifedipine Reduces Vasoconstriction to Endothelin-1 in Essential Hypertension

In 9 healthy subjects (normotensive subjects, age: 48.3+/-7.6 years; blood pressure: 118+/-8.6/69+/-5.4 mm Hg) and 21 patients with essential hypertension (age: 50.0+/-7.8 years; blood pressure: 164.4+/-5.4/103.8+/-4.4 mm Hg), we studied forearm blood flow and its modification induced by intrabrachial administration of endothelin-1, phenylephrine, acetylcholine, and sodium nitroprusside at baseline and after 24 weeks of treatment with a nifedipine gastrointestinal therapeutic system (30 to 60 mg per day). At baseline, the first dose of endothelin-1 (0.5 microg/100 mL of forearm tissue per minute) caused a slight vasodilatation in normotensives but not in hypertensive subjects, whereas the following higher doses caused a comparable dose-dependent vasoconstriction in hypertensives and normotensives. The effect of acetylcholine was significantly reduced in patients with essential hypertension as compared with normotensive subjects. In contrast, sodium nitroprusside and phenylephrine had similar effects in both groups. After chronic treatment with the nifedipine gastrointestinal therapeutic

system, the vasoconstrictor effect induced by both endothelin-1 and phenylephrine was significantly blunted, whereas the response to acetylcholine was significantly increased and the vasodilation to sodium nitroprusside unchanged. In conclusion, this study showed as in patients with essential hypertension, chronic treatment with a long-acting dihydropyridine calcium antagonist not only exhibits a blood pressure-lowering effect but also reduces the vasoconstriction induced by endothelin-1 and improves endothelium-dependent vasodilation. Those vasculoprotective effects may importantly contribute to a reduction in major clinical events seen during treatment with these compounds.[1]

2. Angiotensin converting enzyme Inhibition improves vascular function in rheumatoid arthritis

Patients with rheumatoid arthritis are characterized by increased cardiovascular risk. Angiotensin-converting enzyme inhibitors are proven to exert a beneficial effect in patients with atherosclerotic vascular disease. In view of the similarities between atherosclerosis and rheumatoid arthritis, we planned to evaluate the impact of treatment with ramipril on endothelial function as well as on markers of inflammation and oxidative stress in normotensive patients with rheumatoid arthritis.

We included eleven patients with rheumatoid arthritis in this randomized, double-blind, crossover study. The patients received ramipril in an uptitration design (2.5 to 10 mg) for 8 weeks followed by placebo, or vice versa, on top of standard antiinflammatory therapy. Endothelial function assessed by flow-mediated dilation of the brachial artery, markers of inflammation and oxidative stress, and disease activity were investigated at baseline and after each treatment period.

Endothelial function assessed by flow-mediated dilation increased from 2.85±1.49% to 4.00±1.81% (P=0.017) after 8 weeks of therapy with ramipril but did not change with placebo (from 2.85±1.49% to 2.84±2.47%; P=0.88). Although systolic blood pressure and heart rate remained unaltered, diastolic blood pressure decreased slightly from 78±7 to 74±6 mm Hg (P=0.03). Tumor necrosis factor-a showed a significant inverse correlation with flow-mediated

dilation (r=0.408, P=0.02), and CD40 significantly decreased after ramipril therapy (P=0.049).

In conclusions we demonstrated as angiotensin-converting enzyme inhibition with 10 mg/d ramipril for 8 weeks on top of current antiinflammatory treatment markedly improved endothelial function in patients with rheumatoid arthritis. This finding suggests that angiotensin-converting enzyme inhibition may provide a novel strategy to prevent cardiovascular events in these patients. [2]

3**. Acetaminophen increases Blood Pressure in Patients with Coronary Artery Disease**

In 33 patients with coronary artery disease we evaluated 24-hour ambulatory blood pressure, heart rate, endothelium-dependent and -independent vasodilatation, platelet function, endothelial progenitor cells, markers of the renin-angiotensin system, inflammation, and oxidative stress before and after 2-week treatment with paracetamol (1 g TID) and placebo on top of standard cardiovascular therapy. Treatment with paracetamol resulted in a significant increase in mean systolic (from 122.4±11.9 to 125.3±12.0 mm Hg P=0.02 versus placebo) and diastolic (from 73.2±6.9 to 75.4±7.9 mm Hg P=0.02 versus placebo) ambulatory blood pressures. On the other hand, heart rate, endothelial function, early endothelial progenitor cells, and platelet function did not change.

Our data demonstrate for the first time that paracetamol similarly to other drug used to reduce pain, induces a significant increase in ambulatory blood pressure in patients with coronary artery disease.[3]

“As to diseases, make a habit of two things to help, or at least, to do no harm.”

Hippokrates

1.0 Introduction

Blood flows from heart through the arteries, capillaries, and finally veins back to the heart. The blood pressure is the force that allows this vital flow.

The importance of blood pressure is underlined by the existence of an extremely precise and complex control system involving the autonomic nervous system, the kidney and several hormones.

The arteries and the veins are also important for the blood pressure control. Dysfunctional vessels lead to an increase in blood pressure starting a dangerous vicious circle.

The pathological elevation of arterial blood pressure is a „silent killer“ leading to cardiovascular diseases. In 2008 in Switzerland 22’321 persons died for cardiovascular diseases and arterial hypertension is one of the most important cardiovascular risk factor.[4]

In a general swiss population 23% of men and 21% of women were aware of being hypertensive. At the age of 55-64 years this prevalence rise up to 39% (men) and 32% (women) and at the age of 65-74 years 44% of the men and 46% of the women were hypertensive. Many persons are indeed hypertensive but they are not aware of this problem.[5]

Blood pressure should be regularly checked and if elevated, should be reduced by life-style changes or drug treatment. Some antihypertensive drugs “just” reduce blood pressure while others seems to have additional beneficial effect beyond lowering blood pressure.

From the other side, we should keep in mind that some useful drugs may induce an elevation of blood pressure.

1.1 Clinical significance of measuring blood pressure and evaluating vessel function

Blood pressure values are an important component of the total cardiovascular risk defined by the presence of different risk factors, organ damage and disease. Several studies have shown that a blood pressure higher than 140/90 mmHg is associated with increased cardiovascular morbidity and mortality and reducing blood pressure values under this threshold by life-style modification or drug treatment significantly reduces fatal and non-fatal cardiovascular events.

An impaired vessel function, measured as a reduced endothelial function or an increased arterial stiffness, was found to be associated with arterial hypertension [6, 7] as well as with other cardiovascular risk factors.[6, 8-10] Moreover, the presence of this vascular impairment has a negative prognostic value in patients with cardiovascular risk factors or cardiovascular diseases.[6, 8, 11]

1.2 Methods used to evaluate endothelial function

The acknowledgment of the central role played by the endothelium in the atherothrombotic process led to the development of a wide range of methods for assessing endothelial function in vivo. The aim was not only exploring the patho-physiologic mechanisms underlying atherothrombosis but also using endothelial function as an early clinical marker of the disease and to assess the response to medical interventions.

The most used invasive methodologies include the evaluation of the coronary response to endothelial agonists/antagonists or to physical manoeuvres like cold pressure test and the evaluation of endothelial function in the microcirculation of the forearm by strain gauge plethysmography.[12] The invasive methods allow us to examine the potential mechanisms underlying endothelial dysfunction and the improvement of endothelial function induced by pharmacological and non-pharmacological interventions. At the present

time the flow-mediated dilatation of the brachial artery is considered the gold standard within the non-invasive methods for evaluating endothelial function in vivo.[8] Other methods are measurements of the changes in augmentation index or in reflective index induced by drugs such as beta$_2$-agonists or the pulse amplitude tonometry.[8, 12]

Endothelial function in patients with arterial hypertension

The vascular endothelium plays a fundamental role in modulating vascular tone and structure. Physiological production of vascular relaxing factors, including “nitric oxide”(NO), “prostacyclin” and “hyperpolarizing relaxing factor” protect the vessel wall by antagonizing the initial pathological steps of atherosclerosis and thrombosis.(Figure 1) At the same time the endothelium produces also vasoconstrictors such as endothelin-1, prostanoids.(Figure 1) Alterations in endothelial function are detectable in experimental and human hypertension, however, these changes and the underlying mechanisms are not uniform in different models of hypertension nor in different vascular beds.[13]

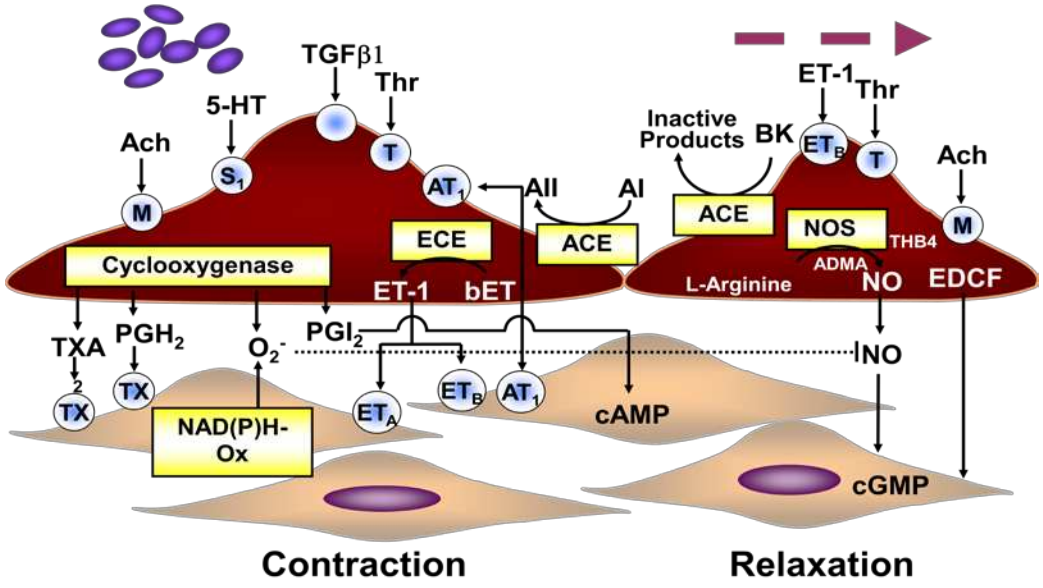

Figure 1: **Vasoactive substances produced by the endothelial cells:** ACh: acetylcholine; 5HT: serotonin; ET$_1$: Endothelin$_1$, BK: bradykinin; AI: Angiotensin I, AII: Angiotensin II, ACE: Angiotensin Converting Enzyme, TGF-β_1: Transforming Growth Factor-β_1, Thr: Thrombin, AT1: Angiotensin Receptor$_1$, bET: big Endothelin, ECE: Endothelin Converting Enzyme, NO: nitric oxide, NOS: nitric oxide synthase; L-Arg: L-Arginine, ET$_A$: Endothelin-Receptor-A, ET$_B$: Endothelin-Receptor-B, PGH$_2$: ProstaglandinH$_2$: PGI$_2$:

Prostacyclin, THB4: Tetrahydrobiopterin, ADMA: asymmetric dimethylarginine; TXA: thromboxane; NAD(P)HOx: NAD(P) Oxidase.

In human hypertension the mechanisms appear to be different at various stages of the hypertensive process and somehow endothelial dysfunction precedes the development of hypertension as normotensive offspring of hypertensive parents exhibit impaired endothelium-dependent vasodilatation to acetylcholine. Moreover, in patients with manifest hypertension and in normotensive offspring, vasoconstriction due to inhibition of NO synthesis is decreased, indicating a reduced basal NO bioavailability.[13] Although the haemodynamic factor plays an important role, the reduction of blood pressure per se does not induce a modification in endothelial function in hypertensive patients.[14, 15]

2.0 Effect of antihypertensive drugs on endothelial function

With regard to the endothelial function different effect can be exerted by different antihypertensives. Calcium-antagonist such as nifedipine may improve endothelial function in the coronary circulation[16] and in the forearm circulation of hypertensive patients.[1] Moreover, it is of note that in normotensive subjects, where the production of nitric oxide is preserved, the effect of endothelin-1 in maintaining vascular tone is very modest, whereas in hypertensive patients, where nitric oxide bioavailability is reduced, a vasoconstrictor component of endothelin-1 seems to be much more evident. Interestingly, nifedipine non only increases the vasodilating response to acetylcholine but also reduces the vasoconstriction by endothelin-1 in essential hypertensive patients.(Figure 2)[1]

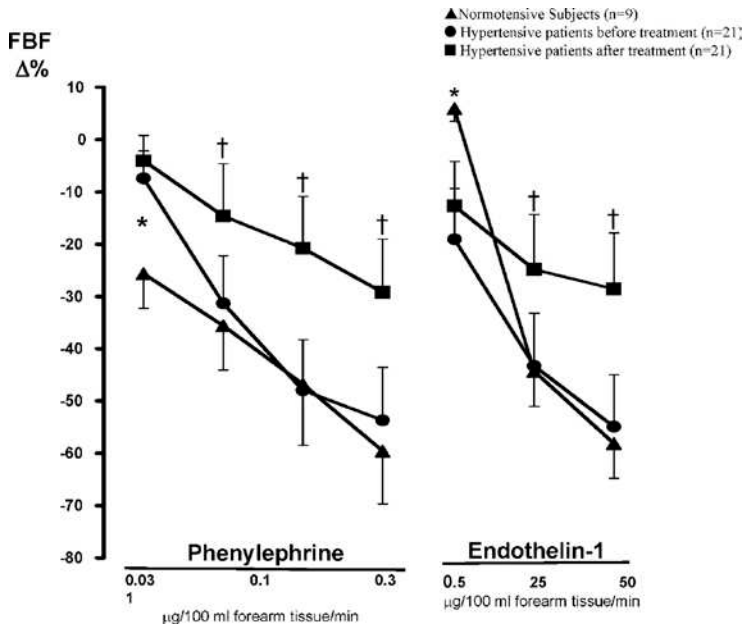

Figure 2 Forearm blood flow (FBF) responses (D%) to Endothelin(ET)-1 and phenylephrine in normotensive subjects (n=9, ▲), and hypertensive patients (n=21) before (●) and after (■) treatment with nifedipine GITS. *P<0.05 or less for normotensive subjects vs hypertensive patients; P<0.05 or less for hypertensive patients before vs after treatment.

Not only calcium-antagonists but also antagonists of the renin-angiotensin system may positively influence endothelial function in patients with arterial hypertension.[13] However, the beneficial effect of this pharmacological class seems to be not only limited to patients with arterial hypertension.

Patients with rheumatoid arthritis are characterized by high cardiovascular risk, possibly due to inflammation and these patients are characterized by impaired endothelial function.[17, 18]

Indeed, we recently demonstrated that the angiotensin-converting enzyme inhibitor, ramipril, improves endothelial function in patients with rheumatoid arthritis and normal blood pressure values.(Figure 3)[2]

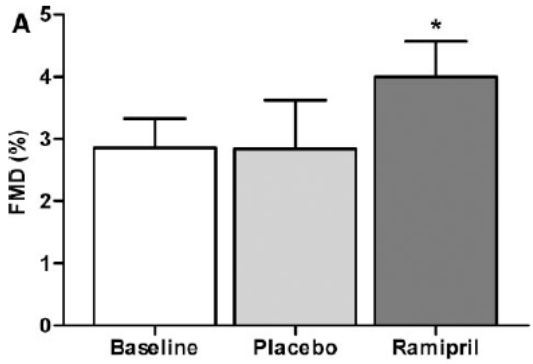

Figure 3: Endothelial function measured as flow-mediated vasodilatation (FMD) of the brachial artery at baseline and after treatment with ramipril and placebo. Asterisks indicate a statistically significant difference (P<0.05) ramipril vs baseline.

3.0 Effect of non-cardiovascular drugs on cardiovascular system

The Food and Drug Administration warns patients with cardiovascular disease to use Cyclooxygenase-2 (COX-2) selective inhibitors and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in view of the potential of these agents to increase adverse cardiovascular outcomes. Nevertheless, millions of patients worldwide require pain-relieving therapy to maintain an acceptable quality of life, the uncertainty around the cardiovascular safety of those drugs leaves practitioners and patients with difficult management decisions.[3]

Current guidelines recommend paracetamol as the first-line analgesic of choice for the management of chronic pain despite weaker analgesic potency on the assumption of its greater cardiovascular safety, particularly in patients at high cardiovascular risk or with established cardiovascular disease.[19]

One of the most commonly used drugs worldwide, a major ingredient in numerous cold and flu medications and commonly used even in children and pregnant women, paracetamol was considered safe, within therapeutic doses. [3, 19]

The link between paracetamol and cardiovascular risk factors or events were explored by a limited number of observational [20-22] and interventional studies[23-25] and the results are so far inconsistent.

In a recently published, randomized, placebo-controlled, cross-over trial we assessed 24-hour blood pressure and endothelial function in 33 patients with stable coronary artery diseases before and after treatment with paracetamol 3gr/day or placebo. This study for the first time demonstrates a significant increase in ambulatory blood pressure in patients with coronary artery disease treated with paracetamol. (Figure 4)[3]

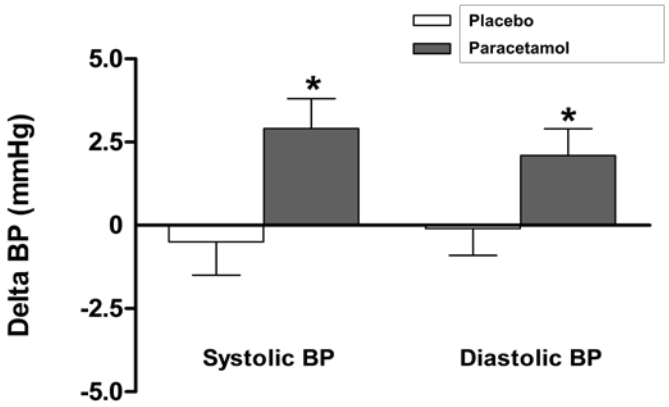

Figure 4: Difference in mean 24-hour ambulatory blood pressure (Delta BP, mm Hg) between baseline and treatment with paracetamol (grey bars) and placebo (open bars). Data are presented as mean±SEM. Asterisks indicate a statistically significant difference (P<0.05) paracetamol versus placebo.

The vascular function did not significantly worsen during the two weeks of treatment with paracetamol.

Therefore, the results of the present study question the presumption of acetaminophen's cardiovascular safety suggesting that the effect of paracetamol on cardiovascular morbidity and mortality deserve more attention by the scientific community.

4.0 Conclusions

Blood pressure and vascular function are two important component of the global cardiovascular risk.

We use drug everyday, we should keep in mind that drugs beyond their primary effect may have some positive effects as well as side effects.

The effect of cardiovascular and non-cardiovascular drugs on blood pressure and vascular function is therefore an important clinical and research target aiming to a better protection of our patients.

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